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NON-MELANOMA SKIN CANCER MAY BE A MARKER OF POOR PROGNOSIS IN PATIENTS WITH NON-HODGKIN'S LYMPHOMA

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According to recent results, patients with non-melanoma skin cancers are at increased risk of developing non-Hodgkin's lymphoma (NHL). The prognostic significance of this association is unknown. Two cohorts of patients with a first diagnosis of non-melanoma skin cancer and a subsequent diagnosis of either NHL (n = 170) or colon cancer (n = 435) were established using national cancer registry data in Denmark. Two other cohorts of patients in whom NHL (n = 600) or colon cancer (n = 1,541) was the patients' first known malignancy served as comparison groups. Mortality rates were compared using Cox's regression analysis. Among patients younger than 80 years at NHL diagnosis, a history of non-melanoma skin cancer was associated with significantly increased mortality [relative risk (RR) = 1.54; 95% confidence interval: 1.19–1.99]. This association was present in both men (RR = 1.38; 1.02–1.86) and women (RR = 2.15; 1.31–3.54) and was similar after both major subtypes of non-melanoma skin cancer. Overall, antedating non-melanoma skin cancer had no prognostic significance for colon cancer patients (RR = 1.00; 0.84–1.18). Whatever the underlying mechanism, our observation has potential clinical implications. If substantiated in other settings, NHL patients with prior non-melanoma skin cancer may constitute a subgroup of lymphoma patients in need of particular therapeutic attention. *Int. J. Cancer* 85:639–642, 2000.
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Cohort studies have pointed to an increased occurrence of non-Hodgkin's lymphoma (NHL) among patients with non-melanoma skin cancers (NMSC) (Adami *et al.,* 1995; Frisch *et al.,* 1996; Kahn *et al.,* 1998; Levi *et al.,* 1996). Ultraviolet light has been proposed as a common risk factor that would explain this (Cartwright *et al.,* 1994; Melbye *et al.,* 1996; Zheng *et al.,* 1992), but the nature of the association awaits further characterisation. No previous study has investigated the potential clinical implications of the link between NMSC and NHL. We thus used population-based cancer registry data to study mortality among NHL patients in relation to history of NMSC.

MATERIAL AND METHODS

We identified all patients in the Danish Cancer Registry with a first diagnosis of NMSC under codes 1911–1919, according to a detailed national modification of the 7th revision of the International Classification of Diseases (ICD-7) and a subsequent diagnosis of NHL, including patients with the phenotypic variant chronic lymphocytic leukemia (CLL) (Harris *et al.,* 1994) (ICD-7 groups 200 and 202 and ICD-7 code 2040, n = 203 patients) between January 1, 1978 and December 31, 1994. We also identified all patients with a first diagnosis of NMSC and a subsequent diagnosis of colon cancer (ICD-7 group 153, n = 493 patients). These patients were chosen as the comparison group since current evidence suggests that NMSC and colon cancer are etiologically unrelated (Schottenfeld and Winawer, 1996). Only patients who survived until the month following NHL/CLL (n = 170, referred to as the exposed NHL/CLL cohort) or colon cancer (n = 435, exposed colon cancer cohort) were included in the analyses (Table I).

For each member of the exposed cohorts, we identified up to 4 NHL/CLL or colon cancer patients in the cancer registry, individually matched on 4-digit ICD-7 code, sex, age (+/− 2 years) and date of diagnosis (+/- 2 years) and for whom NHL/CLL or colon cancer was the first cancer registered. Overall, 675 NHL/CLL patients were identified, of whom 75 did not survive until the month following NHL/CLL. Thus, we were left with 600 NHL/CLL patients for follow-up (unexposed NHL/CLL cohort). Of 1,732 individually matched colon cancer patients without prior cancer, some 1,541 patients entered follow-up the month after diagnosis of colon cancer (unexposed colon cancer cohort) (Table I).

All patients were followed for up to 10 years from the month following their NHL/CLL or colon cancer or until death, emigration, disappearance or December 31, 1994, whichever came first. The impact of antedating NMSC on overall mortality was assessed using Cox's proportional hazard regression analysis (Clayton and Hills, 1993). Analyses were adjusted for sex, age (< 45, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, ≥ 90 years) and calendar period of diagnosis of NHL/CLL or colon cancer (1978–1982, 1983–1987, 1988–1994). Adjustments were also made for stage at diagnosis for NHL/CLL patients within ICD-7 groups 200 and 202 and for colon cancer patients (localised, non-localised or unknown), whereas no meaningful stage categorisation was possible for patients with CLL (ICD-7 code 2040) (Table I).

We studied different subsets of NHL/CLL and colon cancer patients as defined by sex, age at diagnosis (< 80, ≥ 80 years), time since NMSC at diagnosis of NHL/CLL or colon cancer (< 1, 1–4, ≥5 years) and stage at diagnosis [excluding patients with CLL (ICD-7 code 2040)].

Estimates of the risk associated with prior NMSC for different subsets of patients were compared using likelihood ratio tests (Clayton and Hills, 1993). We also evaluated the impact on mortality of type of NMSC, *i.e.,* squamous cell carcinoma (histology codes 80513–80523, 80703–80763, 80943 or 85603, according to the International Classification of Diseases for Oncology) and other types of NMSC, referred to as basal cell carcinoma, of which more than 95% were variants of basal cell carcinoma (histology codes 80903–80933) (Table II).

Initially, we analysed NHL/CLL patients within ICD-7 groups 200 and 202 in one analysis and those with ICD-7 code 2040 in another. Since estimates of relative mortality associated with prior NMSC did not differ statistically between these subsets of NHL/CLL patients, we combined them to increase statistical power, retaining in the statistical models a variable denoting the NHL/CLL phenotype (ICD-7 groups 200 or 202 *vs.* ICD-7 code 2040).

RESULTS

The stage distribution at diagnosis was similar in assessable exposed and unexposed NHL patients, whereas exposed colon

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TABLE I – SELECTED CHARACTERISTICS OF THE STUDIED COHORTS

Characteristic	NHL				Colon cancer	
	ICD-7 groups 200 and 202		ICD-7 code 2040		ICD-7 group 153	
	Exposed (%)	Unexposed (%)	Exposed (%)	Unexposed (%)	Exposed (%)	Unexposed (%)
Gender						
Men	64 (64.0)	227 (63.4)	52 (74.3)	177 (73.1)	251 (57.7)	881 (57.2)
Women	36 (36.0)	131 (36.6)	18 (25.7)	65 (26.9)	184 (42.3)	660 (42.8)
Age group (in years)						
<50	4 (4.0)	14 (3.9)	2 (2.9)	8 (3.3)	2 (0.5)	8 (0.5)
50–59	14 (14.0)	54 (15.1)	3 (4.3)	12 (5.0)	16 (3.7)	65 (4.2)
60–69	19 (19.0)	66 (18.4)	8 (11.4)	37 (15.3)	76 (17.5)	312 (20.3)
70–79	36 (36.0)	143 (39.9)	31 (44.3)	106 (43.8)	192 (44.1)	666 (43.2)
80–89	24 (24.0)	73 (20.4)	19 (27.1)	65 (26.9)	130 (29.9)	443 (28.8)
≥90	3 (3.0)	8 (2.2)	7 (10.0)	14 (5.8)	19 (4.4)	47 (3.1)
Period[1]						
1978–1982	10 (10.0)	36 (10.1)	7 (10.0)	24 (9.9)	29 (6.7)	101 (6.6)
1983–1987	34 (34.0)	121 (33.8)	33 (47.1)	115 (47.5)	94 (21.6)	315 (20.4)
1988–1994	56 (56.0)	201 (56.2)	30 (42.9)	103 (42.6)	312 (71.7)	1125 (73.0)
Time since skin cancer[2] (years)						
<1[3]	27 (27.0)	—	17 (24.3)	—	78 (17.9)	—
1–4	48 (48.0)	—	35 (50.0)	—	182 (41.8)	—
≥5	25 (25.0)	—	18 (25.7)	—	175 (40.2)	—
Stage of disease[4]						
Localised	21 (21.0)	78 (21.8)	—	—	81 (18.6)	237 (15.4)
Not localised	40 (40.0)	151 (42.2)	—	—	320 (73.6)	1227 (79.6)
Unknown	39 (39.0)	129 (36.0)	—	—	34 (7.8)	77 (5.0)
Type of skin cancer						
Squamous cell	21 (21.0)	—	15 (21.4)	—	64 (14.7)	—
Basal cell[5]	79 (79.0)	—	55 (78.6)	—	371 (85.3)	—

[1] Calendar period of diagnosis of NHL or colon cancer.–[2] Interval between diagnoses of non-melanoma skin cancer and NHL or colon cancer.–[3] Includes 10 patients with NHL and 5 patients with colon cancer whose non-melanoma skin cancers were diagnosed during the same month as the NHL and colon cancer, respectively.–[4] For colon cancer patients, localised disease includes Dukes' group A and not localised disease includes Dukes' groups B, C and D. Test for differences in distribution of stage at diagnosis between exposed and unexposed NHL patients (ICD-7 groups 200 and 202): $\chi^2 = 0.30$, 2 d.f., $p = 0.86$, and between exposed and unexposed colon cancer patients: $\chi^2 = 8.61$, 2 d.f., $p = 0.01$.–[5] Includes other and unspecified non-melanoma skin cancers.

cancer patients were generally diagnosed at an earlier stage than unexposed colon cancer patients (Table I). Among exposed NHL and colon cancer patients, stage at diagnosis did not vary significantly according to type of NMSC or time since NMSC (data not shown). Among exposed NHL/CLL patients, the proportion of squamous cell carcinomas was higher among those with time since NMSC < 1 year (34.1%) than among those with time since NMSC ≥ 1 year (16.7%). A similar tendency was observed in colon cancer patients; 20.5% squamous cell carcinomas among those with time since NMSC < 1 year *vs.* 13.4% among those with time since NMSC ≥ 1 year.

Exposed NHL/CLL patients survived for shorter periods (median survival = 1.0 year for patients under ICD-7 groups 200 or 202, and median survival = 1.9 years for those under ICD-7 code 2040) than unexposed NHL/CLL patients (median survival = 1.7 years and 2.7 years, respectively) (Fig. 1*a*, *b*). Exposed and unexposed colon cancer patients had almost identical survival curves, with median survival = 2.0 years in both cohorts (Fig. 1*c*).

Overall, a history of NMSC was associated with significantly increased mortality after NHL/CLL (RR = 1.32) (Table II). Although the impact of prior NMSC on mortality was stronger among women (RR = 1.59) than men (RR = 1.22), this difference was not statistically significant ($p = 0.28$) (Table II). No measurable excess mortality associated with history of NMSC was found among the oldest (≥ 80 years) patients (RR = 0.96), so further characterisation of the association between history of NMSC and mortality after NHL or colon cancer was restricted to those 69% of exposed NHL/CLL patients (n = 117) and 73% of unexposed NHL/CLL patients (n = 440), as well as to those 66% of exposed colon cancer patients (n = 286) and 68% of unexposed colon cancer patients (n = 1051), who were below 80 years at diagnosis.

Compared with unexposed patients, mortality was significantly higher among exposed NHL/CLL patients with time since NMSC < 1 year (RR = 1.70) and 1–4 years (RR = 1.54) and remained increased, yet insignificantly so, for longer intervals between NMSC and NHL/CLL (RR = 1.36) (Table II).

The impact of antedating NMSC on mortality after NHL/CLL was similar for squamous cell carcinoma (RR = 1.75) and basal cell carcinoma (RR = 1.51) (Table II). Among NHL/CLL patients with prior squamous cell carcinoma, mortality tended to be higher among those with time since NMSC < 1 year (RR = 2.69; 95% CI 0.96–7.51) than among those with time since NMSC ≥ 1 year (RR = 1.47; 95% CI 0.72–2.99), although this variation was not statistically significant. Among NHL/CLL patients with prior basal cell carcinoma, no similar tendency towards higher mortality was associated with short time since NMSC (time since NMSC < 1 year: RR = 1.55; 95% CI 0.95–2.55; time since NMSC ≥ 1 year: RR = 1.49; 95% CI 1.09–2.04).

A history of NMSC was not equally associated with mortality among all NHL/CLL patients. Mortality was particularly increased for NHL/CLL patients with localised disease (RR = 3.05), whereas no significant excess mortality was apparent among exposed NHL/CLL patients with non-localised disease and those with unknown stage (Table II).

In contrast with NHL/CLL patients, a history of NMSC had no overall bearing on mortality among colon cancer patients (RR = 1.00) (Fig. 1, Table II). Indeed, no effect of NMSC on mortality after colon cancer was seen across strata of sex, stage at diagnosis and time since NMSC (Table II). As the only exception, antedating squamous cell carcinoma was associated with higher mortality among colon cancer patients (RR = 1.60) (Table II). As in the case of NHL/CLL patients, mortality was particularly high among exposed colon cancer patients whose squamous cell carcinoma antedated the colon cancer by less than 1 year (RR = 2.88; 95% CI 1.32–6.25).

TABLE II – RELATIVE MORTALITY (PROPORTIONAL HAZARD) ASSOCIATED WITH PRIOR NON-MELANOMA SKIN CANCER IN PATIENTS WITH NHL OR COLON CANCER

Characteristic	NHL		Colon cancer	
	RR[1]	95% CI	RR[1]	95% CI
Overall age (years)	1.32	1.07–1.63	0.99	0.86–1.14
<80	1.54	1.19–1.99	1.00	0.84–1.18
≥80	0.96	0.66–1.40	0.98	0.78–1.23
Men	1.22	0.95–1.57	1.11	0.93–1.32
<80	1.38	1.02–1.86	1.18	0.86–1.61
≥80	0.94	0.59–1.49	1.08	0.88–1.33
Women	1.59	1.07–2.37	0.84	0.68–1.05
<80	2.15	1.31–3.54	0.82	0.59–1.12
≥80	1.01	0.53–1.93	0.86	0.64–1.16
Time since skin cancer[2,3] (years)				
<1	1.70	1.09–2.66	1.11	0.78–1.57
1–4	1.54	1.10–2.17	0.87	0.67–1.12
≥5	1.36	0.80–2.31	1.18	0.90–1.53
Stage of disease[2,4]				
Localised	3.05	1.36–6.84	0.78	0.46–1.31
Not localised[5]	1.31	0.82–2.09	1.03	0.85–1.25
Unknown	1.13	0.63–2.03	1.31	0.69–2.49
Type of skin cancer[2]				
Squamous cell	1.75	0.98–3.13	1.60	1.06–2.40
Basal cell[6]	1.51	1.15–1.99	0.95	0.79–1.14

[1]All estimates are adjusted for age (in 5-year age groups), calendar period of diagnosis of NHL or colon cancer (1978–1982, 1983–1987, 1988–1994), sex and stage at diagnosis (localised, not localised, unknown).–[2] Analyses restricted to men and women < 80 years at diagnosis of NHL or colon cancer.–[3] Interval between diagnosis of non-melanoma skin cancer and NHL or colon cancer.–[4] Patients with chronic lymphocytic leukemia (ICD-7 code 2040) are not included in this analysis due to lack of meaningful stage categorisation.–[5] For colon cancer patients, this group includes patients registered with Dukes' groups B, C and D.–[6] Includes other and unspecified non-melanoma skin cancers.

DISCUSSION

The occurrence of NHL among patients with NMSC is increased (Adami *et al.*, 1995; Frisch *et al.*, 1996; Kahn *et al.*, 1998; Levi *et al.*, 1996). Interest in these findings has primarily focused on the suggestion of possible aetiological similarities between these cancers (Cartwright *et al.*, 1994; Melbye *et al.*, 1996; Zheng *et al.*, 1992). Our present results suggest that the NMSC-NHL association may also have clinical implications, inasmuch as a history of NMSC was associated with significantly increased mortality among the large subgroup of patients diagnosed with NHL/CLL before the age of 80 years.

Patients with NMSC have relative survival rates that are only slightly lower than those of comparable age groups in the population at large (Clemmensen and Storm, 1993), so NMSC-related deaths appear only to have contributed marginally to the excess mortality among NHL/CLL patients with antedating NMSC. However, other potential limitations should be considered. Surveillance bias could have produced these results if unspecific symptoms from incipient lymphomas with particularly poor prognosis lead to a closer contact with the health care system and thus to diagnosis of NMSCs that would otherwise have escaped clinical attention. However, we consider this unlikely, since mortality was increased even among NHL/CLL patients whose NMSC antedated the diagnosis of NHL/CLL by several years. During such prolonged periods, we would expect most incipient cases of NHL/CLL to have become clinically manifest. In view of the generally unfavourable prognosis for NHL patients (Storm and Clemmensen, 1993) diagnostic delay also appears to be an implausible explanation since, in that case, we would have expected patients with NMSC to be diagnosed at later stages than patients without NMSC. No such variation in stage was apparent among NHL patients, and colon cancer patients with prior skin cancers were actually diagnosed at earlier stages than those without.

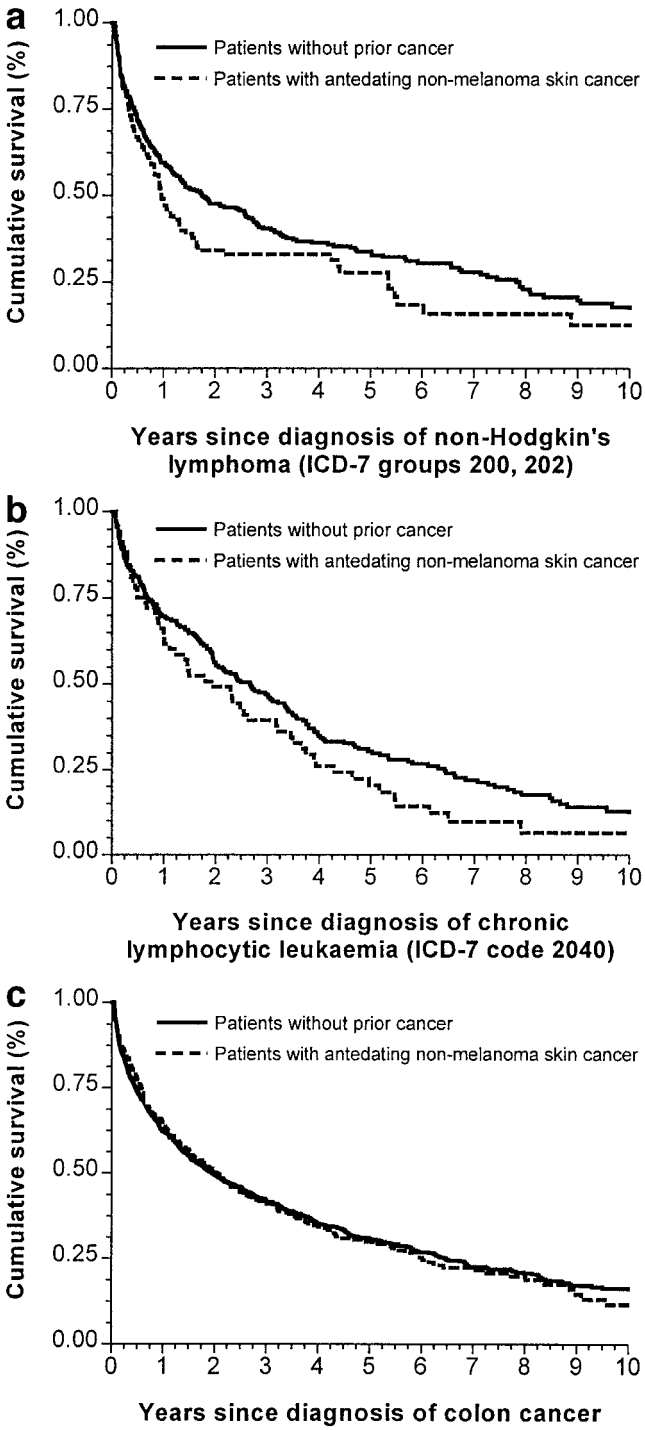

FIGURE 1 – Kaplan-Meier plots showing 10-year cumulative survival after diagnosis of (*a*) non-Hodgkin's lymphoma (ICD-7 groups 200, 202), (*b*) chronic lymphocytic leukemia (ICD-7 code 2040) or (*c*) colon cancer among patients with and without a history of non-melanoma skin cancer.

The influence of factors that might be associated both with increased risks for NMSC and NHL and with increased overall mortality should be considered. Thus, the group of NHL/CLL patients with NMSC could include patients with considerably increased mortality for reasons not specifically related to NMSC or NHL/CLL. States of cellular immune dysfunction, *e.g.*, organ transplantation (Birkeland *et al.*, 1995), could be one such confounder. Our study

does not permit an evaluation of this potential limitation, since organ transplantation and other morbidity data were not available. Still, less than 10% of Danish NHL patients have been hospitalised prior to NHL for diseases known to affect the immune system (Mellemkjær, 1996), so confounding by underlying states of immune dysfunction appears to be an insufficient explanation for the excess mortality observed among NHL/CLL patients with NMSC.

The ratio of squamous cell carcinoma to basal cell carcinoma is increased in patients with cellular immune incompetence (Hartevelt *et al.*, 1990), which suggests that particularly squamous cell carcinoma may be a marker of underlying cellular immune incompetence. Interestingly, we observed that not only NHL/CLL patients but also colon cancer patients with prior squamous cell carcinomas had a poor prognosis and particularly so if the time since the squamous cell skin cancer was short. If the occurrence of squamous cell carcinoma truly reflects cellular immune incompetence, transient or permanent, then cancer patients with prior squamous cell carcinoma would plausibly have higher mortality than other patients. We are currently investigating this possibility.

Radiotherapy for NMSC may be associated with immune modulation (Order, 1977). Consequently, radiotherapy may in theory be one underlying mechanism explaining our present observations. If so, our observations would be of relevance not only for cancer patients with antedating skin cancer but also for cancer patients with histories of other conditions treated with radiotherapy.

Stage at diagnosis is a major determinant of prognosis, and any association of cancer mortality with prior NMSCs should be viewed in light of the stage distribution among the groups of patients studied. We adjusted for potential confounding by stage in localised, non-localised or unknown stage, a subdivision that is unlikely to have been subject to major misclassification. Reassuringly, stage distributions were quite similar for exposed and unexposed NHL patients, and colon cancer patients with prior NMSCs were even diagnosed at earlier stages than unexposed patients.

Among both NHL/CLL and colon cancer patients with time since NMSC < 1 year, squamous cell carcinoma constituted a larger proportion of all NMSCs than the previously estimated proportion of 13% based on all NMSCs registered in Denmark during the period 1978–1989 (Frisch and Melbye, 1995). Recalling the increased ratio of squamous cell carcinomas to basal cell carcinoma in states of immune incompetence, we speculate that a proportion of NMSCs in those patients with short interval between NMSC and NHL/CLL or colon cancer may have been triggered by incipient systemic malignancies.

Even in the Danish Cancer Registry, whose registration is believed to be almost complete for cancers at most sites (Storm *et al.*, 1997), NMSCs may be considerably underreported (Frentz *et al.*, 1994). However, when studying subsequent outcomes (death or subsequent non-cutaneous malignancies, for which the cancer registration is virtually complete), selection mechanisms that would preclude generalisation to all NMSCs in the population are hard to conceptualise. Our observation that NMSC may serve as a marker of poor prognosis after NHL/CLL is therefore unlikely to be influenced by underregistration of NMSCs.

We speculate that social status might contribute to the observed effect of antedating NMSC on survival after NHL/CLL. In the present analyses, we did not have access to information on social status of the patients, but we find social status an unlikely explanation for our observations. Thus, in theory the association between social status and the risk for registered NMSC can work in both directions, *e.g.*, via exposure to UV-light in outdoor occupations (low social status) or exposure to UV-light in connection with leisure time (high social status) (Goldberg, 1996; Marks, 1996).

An increased incidence of NHL among patients with NMSC has been documented (Adami *et al.*, 1995; Frisch *et al.*, 1996; Kahn *et al.*, 1998; Levi *et al.*, 1996). In continuation hereof, we show that NHL/CLL patients with antedating NMSC have a significantly worse prognosis than other NHL/CLL patients. The mechanism underlying this observation is not clear, and confirmatory studies are clearly warranted. If substantiated in other settings, however, NHL/CLL patients with prior NMSC may constitute a subset of lymphoma patients in need of particular therapeutic attention. Meanwhile, our study stresses the importance of vigilance in examining even vague and non-specific extracutaneous symptoms in patients with NMSC, since such skin cancers may be a first and unsuspected sign of an underlying systemic malignancy in a small proportion of patients.

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